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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,724	05/24/2006	**Elisabeth Binder**	009848-0326263	9376

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,724	BINDER ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *3-7,21,22 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8* is/are rejected.

7)☒ Claim(s) *9-20 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I in the reply filed on 10/7/08 is acknowledged. Applicant further elected the species of classifying as predicting the response to therapy, and SNP species rs4713916 and associated oligonucleotides. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-2, 8-20, and 23 read on the elected invention.

3. Claims 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 23 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, and 8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims are drawn to a method of classifying an individual comprising analyzing the nucleic acid of a sample taken from said individual. The claimed invention falls within an enumerated statutory category, namely a process.

In re Bilski No. 2007-1130 (Fed Cir. October 30, 2008) characterizes its machine-transformation test as "the governing test for determining patent eligibility of a process under section 101." Under this test, a process claim is patent-eligible if (and as applied in Bilski

apparently only if): "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." The claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing.

None of the rejected claims requires the transformation of an article or physical object to a different state. For example, one could analyze the nucleic acid of a sample taken from an individual the analysis of a previously recorded sequence from that sample, for example by computer analysis. Additionally, there is no result tied to the physical world. There is no transformation of an article or physical object to a different state. Transformation of data is not considered a physical transformation.

As clearly noted in In re Comiskey No. 2006-1286 (Fed. Cir. Sept. 20, 2007), "the Supreme Court has reviewed process patents reciting algorithms or abstract concepts in claims directed to industrial processes. In that context, the Supreme Court has held that a claim reciting an algorithm or abstract idea can state statutory subject matter only if, as employed in the process, it is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, or composition of matter. 35 U.S.C. § 101." In In re Comiskey, the PTO noted, "[t]he Supreme Court has recognized only two instances in which such a method may qualify as a section 101 process: when the process 'either [1] was tied to a particular apparatus or [2] operated to change materials to a 'different state or thing.''" (quoting Flook, 2006-1286 17 437 U.S. at 588 n.9). In Diehr, the Supreme Court confirmed that a process claim reciting an algorithm could state statutory subject matter if it: (1) is tied to a machine or (2) creates or involves a composition of matter or manufacture. 450 U.S.

at 184. There, in the context of a process claim for curing rubber that recited an algorithm, the Court concluded that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." Id. (quoting Benson, 409 U.S. at 70);13 see also In re Schrader, 22 F.3d 290, 295 (Fed. Cir. 1994) (holding when a claim does not invoke a machine, "§ 101 requires some kind of transformation or reduction of subject matter").

Finally, the Comisky opinion states that mental processes- or processes of human thinking- standing alone are not patentable even if they have practical application. The Supreme Court has stated that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67 (emphasis added). In Flook the patentee argued that his claims did not seek to patent an abstract idea (an algorithm) because they were limited to a practical application of that idea-updating "alarm limits" for catalytic chemical conversion of hydrocarbons. 437 U.S. at 586, 589-90. The Court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that "[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula." Id. at 590.

There is no recitation in the claims of producing a real-word result that is tied to a machine or apparatus or causes a transformation of an article. In other words, the outcome of the rejected methods lack a tie to the machine or apparatus and lack a physical transformation. Thus the claims are rejected as encompassing non-statutory subject matter.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Binder et al. (Abstracts for the Xth World Congress of Psychiatric Genetics, October 2002, abstract labeled O107, pages 752-753).

7. Binder et al. teach a method which comprises analyzing the nucleic acid of a sample taken from an individual for nucleotide polymorphisms in the gene encoding FKBP51 (referred to therein as FKBP5). Namely they teach that polymorphism screening was performed using

capillary electrophoresis single strand conformational polymorphism analysis and sequencing. Analysis included up to 1000 base pairs of the 5'untranslated region, intron/exon junctions, and all exons. Thus, the nucleic acid was genomic nucleic acid. Thus, the teachings of Binder et al. anticipate the claimed invention.

8. Claims 1 and 8 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Gerber et al. (WO 03/082210, as provided in IDS).

9. Gerber et al. teach a method which comprises analyzing the nucleic acid of a sample taken from an individual for nucleotide polymorphisms in the gene encoding FKBP51 (referred to therein as FKBP5). Namely they teach that they determined the sequence of coding and non-coding exons and some of the promoter region for FKBP5. Thus, the nucleic acid was genomic nucleic acid. Four polymorphisms were identified in FKBP5 (Table 2). Thus, the teachings of Binder et al. anticipate the claimed invention.

Claim Rejections - 35 USC § 112

10. Claims 1, 2, and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of classifying an individual comprising analyzing the nucleic acid of a sample taken from said individual for nucleotide polymorphisms in a the gene encoding FKBP51 or in a haplotype block comprising the gene encoding FKBP51. Claim 2 particularly recites that individual is a patient suffering from depression, and the "classifying"

consists of or comprises predicting the response to therapy. The use of these methods, therefore, requires the knowledge of a reliable relationship between polymorphisms in FKBP51 of a haplotype block comprising the gene and classification, for claim 2 in particular, classification regarding the response of an individual suffering from depression regarding their response to therapy.

The association of nucleotide polymorphisms with any phenotype is a highly unpredictable endeavor. The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is unpredictable whether any additional polymorphisms exist in the human FKBP51 gene, or in "a haplotype block comprising the gene encoding FKBP51." The haplotype block can contain millions of nucleotides, and a variety of

genes. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with response to therapy in a depressed individual or with any other classification. Thus, the claimed method of classifying individuals, for enablement of the full scope, requires the use of unpredictable and potentially non-existent products, and further associations between these products and phenotypes. In this case, the genus is itself undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with favorable meat quality.

The claims are not limited to the classification of humans, and in particular to the prediction of response to therapy of humans. There is no guidance in the specification as to which of the disclosed SNP or any SNP at all might be found in non-human organisms, and if they are present, which have relationships to phenotypes such that they can be used to provide meaningful classification of non-human individuals. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of different species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides humans. The unpredictability of the interspecies conservation of polymorphic sites is demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that some positions that are

polymorphic in the human gene are not polymorphic in other non-primate animals, and vice versa (p.18950, Fig 1).

The converse line of reasoning demonstrates that just finding a identifying a FKBP51 polymorphism in an animal other than a human does not necessarily mean that a polymorphism in the gene will be predictive of responds to treatment for depression or any other classification. It is possible that an apparent FKBP51 homolog in a non-human animal might not be functionally equivalent to the FKBP51 gene in pigs. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if homologs of the FKBP51 gene were identified and sequenced in other animals, and even if these new FKBP51 genes displayed polymorphisms, one would have to perform a large amount of experimentation to determine whether or not these putative polymorphisms would be indicative of any particular traits in the animals.

Here the examples in the specification teach the finding of significant relationships between response to treatment for depression and SNP in FKBP51. The specification teaches that thee peaks of strong observation were observed with SNP rs4713916, rs1360780, and rs38000373 (¶0153 of specification; numbering provided in publication of application US 2007/0298027). However, in light of the highly unpredictable nature of this experimental area, significant replication of results is required before an observed value can be considered as being sufficient to enable a method of predicting or classifying based on the presence or absence of particular SNP.

The experiments and data provided in the instant specification are also provided and discussed in Binder et al. 2004 (Nature Genetics, Volume 36, Number 12, published online November 21, 2004). There is significant discussion of these results and their reproducibility, or lack thereof in the post filing date art. For example, Tsai et al. (American Journal of Medical Genetics Part B (Neuropsychiatric Genetics 2007 144B:1097-1098) teach that they investigated the association between FKBP5 SNP rs1360780 and antidepressant response in a more homogenous sample of depressed patients treated with a fixed dose of antidepressant, and found no association between the SNP and response to treatment. Tsai et al. provide a number possible reasons why the results were not reproducible including noting that the discrepancy may have resulted from different severity or subtypes of patients studied between the two studies- underlying the premise that an association observed in one population may not be observed in subsequently studied populations. Further Tsai et al. note that in the study of Binder et al. (and therefore in the instant specification) included patients with recurrent depression, and it has been reported that patients with recurrent depression are often prescribed antidepressants other than those that were effective in the previous treatment episodes. Thus, according to Tsai et al, the better antidepressant treatment results observed could result from patients being treated with effective antidepressants, rather than a genetic association between SNP and treatment result. Tsai et al. also note that differences in median age of populations may account for differences in results, as may the possibility that the findings of Binder et al. are chance findings. Tsai et al. teach, years after the filing of the instant application, that replicated studies in larger samples are needed to fully resolve the possible involvement of the rs1360780 polymorphism in antidepressant therapeutic response.

The post-filing date art of Leckman et al. also attempted to confirm the relationships observed in the instant specification and reported by Binder et al. (2004) (Leckman et al. Biol Psychiatry 2008, 63: 1103-1110). Leckman et al. did not observe significant results for remission nor response to antidepression treatment for any of there SNP tested, with the exception of a significant corrected p value for the rs4713916. This observation was significant, however, only in a mixed ethnic group analysis but not when white or black subjects were considered separately (Table 2). These results demonstrate that observations can be population specific and replication is required before any single observation or set of observations is considered robust enough to be the basis for a classification method. Furthermore, Leckman et al. point out that their study and the study presented by Binder et al. both fail to include a positive or negative control for the treatment itself and thus cannot distinguish pharmacological response from placebo response to asses the absolute effect as well as the relative effect.

Papiol et al. (Journal of Affective Disorders 104 (2007) 83-90) teach that they were not able to replicate the results reported by Binder et al. on the relationship between SNP in FKBP5 and influence on clinical response. Papiol et al. teach that SNP for detecting a phenotypic effect in a southern German population might not be the best SNP for detecting the same effect in a Spanish population (p. 89).

Claims 1 and 8 encompass any type of classification based on the presence of SNP, including, for example classification of disease status for depression or any disease. The instant specification teaches that there was no difference between allele frequencies and disease status for the populations studied. Further, Gawlik et al. (BMC Psychiatry 2006, 6:52, six pages) teach that their data do not support a significant genetic contribution of FKBP5 polymorphisms and

haplotypes to affective psychosis. It is highly unpredictable what classifications can be made based on SNP in the FKBP51 gene or haplotype block containing the gene.

An enormous amount of experimentation in a highly unpredictable technology area would be required to determine if, which, and how SNP in the FKBP51 gene or haplotype blocks comprising the gene are predictive of any phenotype, or response to treatment for depression in particular. Experimentation would have to be undertaken to determine which populations the observations reported in the instant specification are repeatable in. The claims encompass prediction in any population of humans or any other animals, and experiments would have to be undertaken to clarify and elucidate which populations are properly classified using which polymorphisms, disclosed or yet to be discovered. All of this experimentation would be carried out with no guarantee of success.

Thus, having carefully considered all of these factors, it is determined that it would require undue experimentation to make and use the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 9:00 AM until 4:30 PM, and Thursday afternoon from 12:30 PM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is

assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

December 30, 2008